

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 05: Depression and Other Mental Health Disorders

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the seven topics for which (1) preliminary phase III data on drugs or phase II or III data on devices and procedures were available or a program innovation was being implemented; (2) information was compiled by September 21, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between December 15, 2011, and October 26, 2012. (Thirty-four topics in this priority area were being tracked in the system as of October 26, 2012.) We present four summaries of four topics (indicated below by an asterisk) that emerged as having some potential for high impact on the basis of experts’ comments. This Executive Summary and report is organized alphabetically by intervention in two sections, one for Devices and Drugs and the other for Program-Based Interventions. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 05: Depression and Other Mental Health Disorders

Topic	High-Impact Potential
1. Acupuncture for treatment of posttraumatic stress disorder	No high-impact potential at this time
2. * Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans	Moderately high
3. * Mifepristone (Korlym) for treatment of psychotic major depression	Moderately high
4. * Deep brain stimulation (Reclaim DBS Therapy or Libra DBS) for treatment-resistant depression	Moderately high
5. * Off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
6. Off-label riluzole (Rilutek) for treatment of major depressive disorder	No high-impact potential at this time
7. Off-label sodium oxybate for the treatment of binge-eating disorder	No high-impact potential at this time

Discussion

One theme common to health interventions being developed for mental health disorders is the search for options to address treatment resistance in disorders such as major depressive disorder (MDD), bipolar disorder, and posttraumatic stress disorder (PTSD). A drug for psychotic major depression (PMD), for which the U.S. Food and Drug Administration (FDA) has not approved any

therapies, is being explored. The proposed use of implanted devices for treating mental health conditions represents a departure from traditional pharmacotherapy and psychotherapy approaches. Also, an approved anesthetic is being investigated for its rapid antidepressant effects, which remains an unmet need in this field. In the absence of optimal, effective strategies for PTSD, a peer-support program captured experts' attention as having high potential to improve support for veterans with PTSD.

Drugs and Devices

Mifepristone (Korlym) for Treatment of Psychotic Major Depression

- **Key Facts:** PMD is a subcategory of MDD and is associated with a higher risk of hospitalization, suicide attempts, and suicides than nonpsychotic MDD. For this condition, no interventions are specifically approved by FDA, and treating this population remains a challenge. Cortisol, a hormone produced by the adrenal gland, mediates the body's response to stress. In patients with PMD, cortisol is secreted at higher rates (hypersecreted) than it is secreted in patients with nonpsychotic MDD, and research has suggested that administering glucocorticoids to healthy participants can induce cognitive deficits similar to those seen in patients with PMD. Because this evidence might point to an etiological and pathophysiological link between cortisol and PMD, cortisol has been proposed as a therapeutic target for PMD. Mifepristone (Korlym[™] [formerly Corlux], Corcept Therapeutics, Inc., Menlo Park, CA) is an oral glucocorticoid-II receptor (GR-II) antagonist that is being investigated for treating PMD; its manufacturer purports that blocking the GR-II receptor might prevent excessive cortisol activity, potentially relieving PMD symptoms. Mifepristone for treating PMD is being investigated in one phase III clinical trial. Three phase III trials did not individually demonstrate statistical superiority of mifepristone over placebo, but the manufacturer asserts this is because of low dosages used in the trials, and it is actively developing mifepristone for this condition in an additional phase III trial.
- **Key Expert Comments:** Experts agreed that the unmet need for effective treatment for PMD is important, especially considering the debilitating nature of this condition and the poor outcomes associated with it. However, experts were divided on whether this intervention will meet that need and are eager to see more data. Experts commented that if proven to be effective for this condition, the drug would improve patient outcomes and could reduce costs of care associated with untreated PMD or treatment-refractory PMD. Based on this input, our overall assessment is that this intervention is in the moderate potential high-impact range.
- **Potential for High Impact:** Moderately high

Deep Brain Stimulation (Reclaim DBS Therapy or Libra DBS) for Treatment-Resistant Depression

- **Key Facts:** Despite availability of oral pharmacotherapy and psychotherapy as first- and second-line therapies and electroconvulsive therapy or repetitive transcranial magnetic stimulation as second- or third-line therapies for MDD, a proportion of patients affected by MDD have treatment-refractory disease. Therefore, investigators are seeking new approaches for treatment-refractory disease. Deep brain stimulation (DBS), which has become an accepted modality to treat some movement disorders (e.g., Parkinson's disease, dystonia), is being explored for treating psychiatric conditions, including MDD. DBS employs a battery-operated, pacemaker-like neurostimulator implanted in the chest below

the clavicle (collarbone) to deliver controlled electrical stimulation to the brain via thin wire electrodes. The electrodes carry a high-frequency electrical signal that interferes with neural activity at the placement site and is intended to inhibit the activity in that region of the brain. Currently, the Reclaim[®] device (Medtronic, Inc., Minneapolis, MN) and the Libra[®] DBS device (St. Jude Medical, Inc., St. Paul, MN) are both in phase III development for DBS for MDD. Reclaim trials for MDD have an anticipated completion date of October 2014; the BROADEN phase III trial of Libra was still recruiting patients as of November 2012. The Reclaim device received humanitarian device exemption approval for obsessive-compulsive disorder, which marked the first FDA approval of any DBS device for a psychiatric indication. DBS is expected to be positioned as an additional second-line therapeutic option.

- **Key Expert Comments:** Experts commenting on this topic believe that DBS could have an impact on several parameters of the health care system, including increased costs, a shift in care setting from outpatient to inpatient, the addition of neurosurgery to the clinical pathway, and barriers to clinical and patient acceptance. Overall, experts were optimistic about the intervention's potential to improve patient outcomes for treatment-refractory disease. A few experts noted that the target population for this intervention is small; this observation tempered their overall assessment of the technology. Based on this input, our overall assessment is that this intervention is in the moderate end of the potential high-impact range
- **Potential for High Impact:** Moderately high

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** Despite widespread use, approved medications for treating bipolar depression do not elicit the desired therapeutic response in many patients and are associated with considerable lag time in response. Only a fraction of patients respond within a week of administration of many of the medications available for bipolar depression and MDD. This delay can increase suicide risk and mortality. Ketamine hydrochloride is a long-used general anesthetic (since 1966) now being investigated with funding from the National Institute of Mental Health for treatment-resistant bipolar depression and MDD. The drug is given during a single intravenous infusion, and preliminary data have indicated it produces a rapid (within 2 hours) and relatively sustained (about 1–2 weeks long) significant reduction in the Hamilton Depression Rating scales in some patients with bipolar depression or MDD.
- **Key Expert Comments:** Overall, experts who commented were highly optimistic about the drug's potential to meet the need for rapid-onset, effective treatment for bipolar depression and MDD. They thought that the drug could have an important impact across many health system parameters, including lowering costs incurred from ineffective treatment, reducing suicide risk because of its rapid action, and changing care setting from outpatient oral therapy prescribed in a physician's office to outpatient infusion therapy administered by a different type of provider in an infusion clinic. However, experts also suggested that barriers to diffusion may exist, stemming from the potential of relapse.
- **Potential for High Impact:** Moderately high

Program-Based Intervention

Citizen Soldier Peer Support Outreach Program (Buddy-to-Buddy) for Returning Veterans

- **Key Facts:** Despite the high number of citizen soldiers who develop PTSD, clinical depression, substance abuse, sleep disturbances, or suicidal thoughts, only about half who need intervention receive care. Therefore, programs have been developed that are intended to link more soldiers to mental health services and support. One of these new programs, the Buddy-to-Buddy program, is a veteran peer-outreach support program that operates by training veterans to provide support and linkage to needed resources for returning civilian soldiers. The program is based on the theory that for returning soldiers, peer-to-peer “buddies” are uniquely positioned to offer emotional support and resources because of the shared experience of war. This, in turn, might help reduce the stigma associated with seeking mental health care.
- **Key Expert Comments:** Experts agreed that the unmet need this program purports to address is vast and important and that this program is likely to meet some of this unmet need, especially for groups of people who are affected by health disparities (e.g., limited access to services, stigma associated with seeking mental health care). However, because the service is designed to link patients to existing services, experts did not believe that that this program would particularly disrupt current health care infrastructure or patient management models, other than potentially increasing patient volume in treatment centers.
- **Potential for High Impact:** Moderately high

Drug and Device Interventions

Mifepristone (Korlym) for Treatment of Psychotic Major Depression

Currently used treatments for psychotic major depression (PMD)—a subcategory of major depressive disorder (MDD) with a higher risk of hospitalization, suicide attempts, and suicides than nonpsychotic MDD—are associated with unwanted side effects, extensive lag time between start of medication and therapeutic effects, suboptimal efficacy, and stigma (especially in the case of electroconvulsive therapy [ECT]).¹⁻³ Furthermore, no interventions are specifically approved by the U.S. Food and Drug Administration (FDA) for treating PMD.⁴ Effective medications are needed for this condition. If approved, mifepristone would be the first pharmacotherapeutic agent indicated for use in this population.

Cortisol, a hormone produced by the adrenal gland, mediates the body's response to stress.^{1,5} In patients with PMD, cortisol is secreted at higher rates (hypersecreted) than it is secreted in patients with nonpsychotic MDD.⁶ Furthermore, research has suggested that administering glucocorticoids to healthy participants can induce cognitive deficits similar to those seen in patients with PMD.⁶ Because this evidence might point to an etiological and pathophysiological link between cortisol and PMD, cortisol has been proposed as a therapeutic target for PMD.⁶

Mifepristone (Korlym[™] [formerly Corlux], Corcept Therapeutics, Inc., Menlo Park, CA) is an oral glucocorticoid-II receptor (GR-II) antagonist that is being investigated for treating PMD.⁷ Cortisol binds to glucocorticoid receptors in the brain, including the GR-II.⁶ Mifepristone's manufacturer purports that blocking the GR-II receptor might prevent excessive cortisol activity, potentially relieving PMD symptoms.⁷ For this condition, mifepristone is being administered orally, in tablet form, once daily, for several days.⁸

Using mifepristone to treat PMD is being investigated in one ongoing phase III clinical trial.⁸ Three phase III trials did not individually demonstrate statistical superiority of mifepristone over placebo.⁷ However, the manufacturer is actively developing mifepristone for this condition, stating the following:

While the studies did not meet their primary endpoints individually, data aggregated from Corcept's major efficacy studies of similar design, involving 724 observed cases, indicate that the response rate in patients who received CORLUX separated from the placebo group with statistical significance for the endpoint, 50% improvement in the BPRS PSS [Brief Psychiatric Rating Scale Positive Symptom Subscale] at Day 7 and at Day 56. In addition, using the same endpoint, the response rates for patients who achieved a drug level in their plasma that was greater than the 1660 nanogram per milliliter threshold mentioned above, statistically separated from both those patients whose plasma levels were below this threshold and those patients who received placebo.⁷

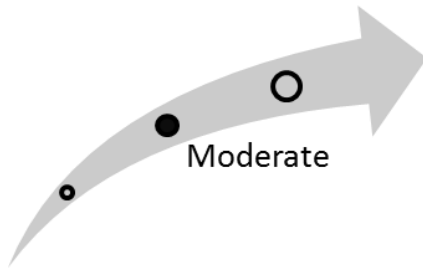
This finding prompted the manufacturer to design its current phase III trial using a higher dose, stating that this change may allow "more patients to achieve higher plasma concentrations of [the] drug and improve the efficacy 'signal.'"⁷ In "Study 14," it is testing a 1,200-mg, once-daily dose given for 7 days. It expects to complete patient enrollment at 20 clinical sites in 2013. FDA has granted the agent fast track status for this indication.²

Clinical Pathway at Point of This Intervention

Although no treatments are FDA-approved for PMD, pharmacotherapy used for MDD is typically first-line treatment involving concomitant use of antidepressant and antipsychotic

medications.^{2,9} For patients who do not respond to pharmacotherapy, ECT is sometimes used.⁹ Mifepristone would likely be positioned as first-line treatment.

Figure 1. Overall high-impact potential: mifepristone (Korlym) for treatment of psychotic major depression



Experts commenting on this intervention agreed that the unmet need for an effective, FDA-approved treatment for PMD is important, especially considering the debilitating nature of this condition and the poor outcomes associated with it. However, experts were divided on whether this intervention will meet that need, with some experts commenting that more data would be necessary before wide adoption could occur. However, experts commented that if the drug is proven to be effective in treating this condition, it could have important impacts on improving patient outcomes and costs of care. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research and health systems backgrounds, provided comments on this topic.¹⁰⁻¹⁵ Experts agreed that the unmet need for interventions for PMD is important, given suboptimal current treatments, the lack of an FDA-approved treatment for this condition, and the condition's debilitating nature. One expert, with clinical experience in treating this patient population stated that treating PMD has been a major challenge, because "the presence of psychotic features (often not identified or diagnosed) is a major reason for treatment resistance in depression" and that treatment remains an important unmet need.¹⁵

Experts had discordant opinions as to whether mifepristone will meet this need, however. On one hand, some experts noted that available trial data are not particularly compelling, given the trial design and outcomes thus far. These experts wanted to see more positive data. On the other hand, one clinical expert, who did additional research into this topic, commented that he finds the available literature compelling and believes that unsatisfactory trial data thus far are a reflection of poor trial design and not necessarily the efficacy of the drug. Another research-based expert pointed out that the FDA fast track designation suggests that this idea may have merit.

Several experts believe that this intervention, if shown to be effective, would have positive effects on health disparities. The treatment would offer a lower-cost and more widely diffusible (compared with ECT) intervention, which may improve access to care for some patients. The agent might also improve the ability of marginalized patients to return to the workforce or otherwise engage in societal interactions, such as seeking medical treatment when necessary.

Experts generally agreed that the oral administration route of the drug would be a benefit, especially when compared with ECT. Experts agreed that virtually no training would be needed to prescribe the intervention and that it would carry markedly less stigma than ECT, which may aid diffusion of the drug if it is approved. For these reasons, experts thought that patients would be extremely accepting of the intervention. Similarly, the experts anticipated that clinicians would readily adopt the intervention, considering the limitations of available treatments. If the drug is

shown to be effective, most experts believe, it would reduce the need for some hospitalizations and the need for (costly) ECT. In light of this, experts agreed that mifepristone has the potential to reduce long-term treatment costs associated with PMD. Experts also noted that any improvement in functional ability in these patients may be associated with reduced societal costs.

Deep Brain Stimulation (Reclaim DBS Therapy or Libra DBS) for Treatment-Resistant Depression

Although medication and psychotherapy are the primary treatments for treatment-resistant MDD, investigators have sought new approaches because available drugs and psychotherapy often fail to control symptoms adequately. One approach, deep brain stimulation (DBS), an established treatment for movement disorders (e.g., Parkinson's disease, dystonia), is being explored as a treatment for psychiatric conditions and is already approved for treating obsessive-compulsive disorder. It is under study for MDD.

DBS therapy uses a battery-operated, pacemaker-like neurostimulator, which a surgeon implants subcutaneously in the patient's chest below the clavicle, to deliver controlled electrical stimulation to the brain via thin wire electrodes.¹⁶ The electrodes carry a high-frequency electrical signal that interferes with the neural activity at the placement site and is intended to inhibit the activity in that region of the brain.¹⁷

Physicians often perform the device implantation in two separate procedures: lead placement and neurostimulator implantation. A neurosurgeon implants electrode leads in the brain using local anesthesia under stereotactic guidance; for this procedure, the patient is usually hospitalized overnight. Neurostimulator implantation is performed under general anesthesia, usually as an outpatient procedure. The electrode leads connect to the neurostimulator through insulated extension wires, which are tunneled under the skin at the scalp and down the neck to the chest. For treating MDD, different clinical investigators and manufacturers are targeting different areas of the brain with their respective DBS devices.¹⁶

About 2–4 weeks after implantation surgery, physicians activate and program the neurostimulator through a wireless programming computer, with followup therapeutic adjustment performed as needed. As instructed by their physicians, patients can turn the neurostimulator on and off with a control magnet. The DBS battery lasts from 6 to 16 months on average, depending on device programming and the frequency of stimulation required. When the battery is depleted, a surgeon must perform a minor surgical procedure to replace the neurostimulator device. In most cases, the new device can be connected to the existing electrode leads.¹⁶

Medtronic, Inc. (Minneapolis, MN), is developing the Reclaim[®] DBS Therapy device, and St. Jude Medical, Inc. (St. Paul, MN), is developing its Libra[®] DBS system for treatment-resistant depression. Reclaim is in a phase III trial under an FDA investigational device exemption (IDE), and Libra is recruiting for an FDA IDE trial.¹⁸⁻²⁰

Investigators concluded from a 2010 Reclaim DBS Therapy trial of 10 patients with severe, treatment-resistant MDD, that “[t]welve months following initiation of DBS treatment, 5 patients reached 50% reduction of the HDRS [Hamilton Depression Rating scale] (responders, HDRS = 15.4 [+/-2.8]).”²¹ According to Medtronic, patients who undergo DBS to treat MDD would face risks similar to those faced by patients who undergo DBS for other indications.

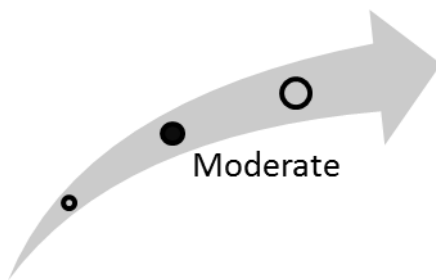
The Libra DBS system trial is known as the phase III BROADEN (Brodmann Area 25 Deep Brain Neurostimulation).²⁰ According to a July 2011 company press release, FDA approved an expansion of the trial to 20 sites across the United States and expanded enrollment to 125 patients.²⁰ As of November 2012, the trial Web site (www.broadenstudy.com) indicated that enrollment remained open.

Clinical Pathway at Point of This Intervention

American Psychiatric Association guidelines for treating MDD recommend a combination of oral pharmacotherapy and psychotherapy. Second-line therapy for MDD includes ECT or transcranial magnetic stimulation (TMS). If approved for this indication, DBS is expected to be positioned as an additional second-line therapeutic option.

Because DBS is invasive in nature, pharmacotherapy and psychotherapy are expected to remain first-line treatments for MDD; DBS is indicated to complement conventional drug therapy. Depending on DBS treatment efficacy in individuals, its use might allow some patients to use lower drug dosages or different drug regimens; however, no data are yet available to support this hypothesis. DBS therapy is incompatible with some other device-based depression treatments. For example, TMS is contraindicated in patients with implanted DBS devices, and the safety of ECT in patients with an implanted DBS system has not been established. Additionally, patients with an implanted DBS system may be unable to undergo procedures that use electrocautery devices or certain types of magnetic resonance imaging exams.

Figure 2. Overall high-impact potential: deep brain stimulation (Reclaim DBS Therapy or Libra DBS) for treatment-resistant depression



Experts commenting on this topic thought that DBS could have an impact on several parameters of the health care system, including increased costs, a shift in care setting from outpatient to inpatient, the addition of neurosurgery to the clinical pathway, and barriers to clinical and patient acceptance. Overall, experts were optimistic about the intervention's potential to improve patient outcomes, but a few noted that the target population for this intervention is small, which tempered their overall assessment of the technology. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the potential impact of DBS for MDD.²²⁻²⁷

Most of the experts agreed that the unmet need for novel, effective interventions for treatment-resistant MDD is very important, given the debilitating nature of the condition and the accompanying societal and financial burdens. However, this opinion was somewhat tempered by the small size of the patient population that does not respond to currently available (first-, second-, or third-line) treatments.

Overall, experts supported the theory underlying use of DBS in these populations, which may reflect their knowledge about the efficacy that DBS has shown in patients with movement disorders. Although most of these experts agreed that available data suggest the intervention shows promise for treating MDD, several offered a caveat, calling for more efficacy data obtained from larger study populations.

The experts asserted that DBS has the potential to markedly disrupt care models, treatment paradigms, and patient management for these patients, not only because it provides a new treatment modality (surgical implant rather than medical and talk therapy), but because it has the potential to shift care from oral pharmacotherapy to neurosurgery. However, several experts stated that because DBS would be indicated for use in only a small subpopulation of patients with MDD, these changes would not dramatically affect the health care system as a whole.

Generally, experts agreed DBS would require changes to staffing mix, care setting, and clinician training practices because the intervention necessitates a shift from medical therapy at home to the neurosurgical operating room and inpatient hospital setting. Several experts noted that this would require much clinician training, although other experts disagreed, stating that neurosurgeons are already familiar with DBS implantation (for movement disorders).

Experts agreed that this intervention would have dramatic cost impacts for the small population for which the treatment is intended. The upfront costs of the device and implantation procedure are significant and may pose a barrier to uptake, especially because few payers cover it at this point. Additionally, battery replacement involves a surgical procedure, which will also be costly. It should be noted that experts commenting tended to compare their cost-change estimates to pharmacotherapy, although DBS is not likely to compete with pharmacotherapy but rather is expected compete with more costly, third-line interventions such as repetitive TMS, ECT, and ablative neurosurgery. Therefore, the expected change in upfront costs might be less significant than these experts believe. Second, experts thought that if DBS were effective at controlling MDD symptoms, it might decrease the significant financial burden of ongoing, uncontrolled MDD.

In terms of patient and clinical acceptance of this procedure, some experts thought the invasiveness and possible side effects of the procedure might be barriers to acceptance, but others thought that patients with intractable MDD would be willing to accept an intervention that potentially could improve symptoms and quality of life, regardless of its invasiveness. Some experts also thought controversy might arise in light of the debate over using neurosurgical interventions for treating MDD.

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Many cases of bipolar depression and MDD are not effectively managed (e.g., fail to respond, do not achieve remission) with currently available pharmacotherapies.²⁸ Also, because available pharmacotherapies have a delayed onset of action and once active, do not exert effects rapidly (i.e., within hours), they are ineffective in managing acute episodes associated with these conditions.^{28,29} Furthermore, available agents are associated with undesirable side effects that may limit adherence to medical treatment in patients with these conditions.²⁸ Therefore, an unmet need exists for novel, effective, fast-acting, and well-tolerated interventions for treating depressive episodes that occur with bipolar disorder or MDD. Glutamate is known to be the major excitatory neurotransmitter in the brain.²⁸ Researchers believe that dysfunction in glutamate neurotransmission may play a major role in the etiology of depressive symptoms in both bipolar disorder and MDD, although its exact mechanism of action is still unknown.^{28,30} Research has suggested that glutamate N-methyl-D-aspartate (NMDA) receptors may mediate this glutamatergic dysregulation, giving rise to the hypothesis that NMDA receptor antagonists may have antidepressant effects.³⁰ Data from both preclinical and clinical studies have suggested that NMDA receptors are viable therapeutic targets to investigate for treating bipolar depression.³⁰

Ketamine hydrochloride (ketamine) is a noncompetitive, high-affinity NMDA antagonist that is approved in the United States for use as a general anesthetic.^{28,31} Now, ketamine is being investigated for the intravenous treatment of depressive episodes in patients with bipolar disorder or MDD.^{28,32} Ketamine has been shown to increase “the firing rate of glutamatergic neurons and the presynaptic release of glutamate” in vitro, and these characteristics may contribute to the agent’s antidepressant effects.²⁸ Clinical trials have shown ketamine to have a rapid (e.g., within minutes or hours) therapeutic effect; research suggests that this rapid effect may be due to the agent’s high affinity for NMDA receptors and to its intravenous administration route.²⁸ In clinical trials for these indications, ketamine is generally administered as a single intravenous infusion, at dosages lower than those used for anesthesia.³² Data from these trials suggested that depressive symptoms improved both significantly and rapidly and that these effects lasted from 3 days to several weeks, following a single infusion.^{29,33,34}

The drug was launched in 1966 by King Pharmaceuticals, now a unit of Pfizer, Inc. (New York, NY), as a general anesthetic agent, and both branded and generic versions are sold by several manufacturers.^{31,35,36} However, it does not appear that the drug’s manufacturers are seeking a labeled indication change. Instead, ketamine’s off-label use in bipolar disorder and MDD is being investigated by research institutions, such as Baylor College of Medicine (Houston, TX), Mount Sinai School of Medicine (New York, NY), National Institute of Mental Health (Rockville, MD), and the National Institutes of Health Clinical Center (Bethesda, MD).³⁷⁻³⁹

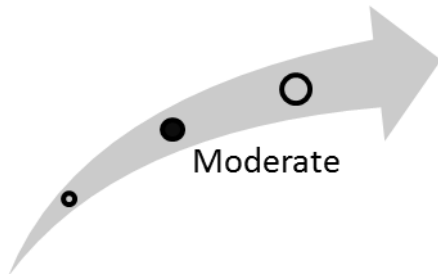
Ketamine is classified as a Schedule III nonnarcotic controlled substance and, at higher doses, is sometimes abused as a street drug (“Special K”), which may affect the regulatory pathway for this indication.^{32,40}

Clinical Pathway at Point of This Intervention

According to the U.S. Department of Veterans Affairs, acute depressive episodes of bipolar disorder are treated with combinations of pharmacotherapy (e.g., quetiapine, lamotrigine, lithium), psychoeducation, and psychotherapy (e.g., counseling). ECT or alternative therapies may be considered.⁴¹ According to the National Institute of Mental Health, MDD is usually treated with

pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) and psychotherapy.⁴² In some cases in which drugs and therapy are not effective, patients may receive ECT, vagus nerve stimulation, or TMS.⁴² If it is determined that ketamine is effective in treating these mood disorders, it is likely to be positioned for treating acute depressive episodes in patients with either bipolar disorder or MDD.²⁸

Figure 3. Overall high-impact potential: off-label ketamine for treatment of bipolar depression and major depressive disorder



Overall, the experts commenting on this material were highly optimistic about this intervention's potential to meet the need for a rapid-onset, effective treatment for depressive episodes associated with bipolar disorder or MDD. They thought that the drug would have an important impact across many health system parameters, including shifting care to the clinical setting and potentially reducing long-term health care costs. However, support for this intervention was somewhat tempered by fact that the drug requires office-based administration and is known to be a street drug of abuse. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.⁴³⁻⁴⁹

The experts strongly agreed that the unmet need for rapidly effective medications for either bipolar depression or MDD is extremely important, citing issues such as prevalence, societal burden of the illness, and lag time for efficacy of current medications. Furthermore, most of the experts were highly optimistic about this agent's ability to meet this need, citing both the underlying mechanism of action and the promising clinical trial data to date. Experts suggested that because of ketamine's rapid efficacy, this agent may be most useful in patients who are experiencing suicidal ideation and are brought to the emergency department.

Experts generally agreed that ketamine would affect the way patients are managed for these conditions because the drug is administered via an infusion and must, therefore, be given by a medical professional. Experts noted that this intervention will shift care (oral pharmacotherapy) from a home to a clinical setting. Even more, experts stated that this would be the first agent that might be able to produce rapid antidepressant effects in patients, which would represent a significant departure from current patient management.

In light of the potential change in care setting, experts noted, this intervention would be likely to affect staffing levels and health care processes for treating this population. That is, patient volume in infusion centers might increase, which, in turn, would require increased staffing to administer the drug and monitor patients. For these reasons, most experts believe, this intervention would increase the per-patient cost of care for this patient populations, although the drug itself is not expected to be particularly costly. Several experts believe that these initial costs of care would be recouped over

time because a rapid-action, efficacious drug might obviate the need for inpatient stays, reduce the frequency of visits to clinician's offices, and move treatment to partial-hospital care settings.

Although the experts all agreed that uptake of this therapy could both influence and be heavily influenced by patient and clinical acceptance, experts were divided on whether acceptance would be broad or narrow. On one hand, some experts thought that patients with treatment-refractory depression would readily accept a novel intervention that has the potential to improve their quality of life, and one clinical expert went so far as to suggest that this will become a "standard practice in emergency departments in the management of suicidal patients."⁴⁷ However, other experts suggested that medication infusion would require more office visits, and could be a barrier to use. Some experts indicated that ketamine is associated with dissociative reactions and that, along with its reputation as a "street drug" with a known risk of abuse may also pose barriers to uptake.

Program-Based Intervention

Citizen Soldier Peer Support Outreach Program (Buddy-to-Buddy) for Returning Veterans

Twenty-five percent to 40% of citizen soldiers (National Guard and Reserves) who were deployed to Afghanistan and Iraq develop posttraumatic stress disorder (PTSD), clinical depression, substance abuse, sleep disturbances, or suicidal thoughts.^{50,51} Of these, only about half receive care.⁵⁰ The Buddy-to-Buddy program is intended to meet the need to link more veterans with appropriate medical and psychological resources.

The Buddy-to-Buddy program, developed at the University of Michigan (Ann Arbor) in partnership with the Michigan Army National Guard (MI ARNG, Lansing) and Michigan State University (East Lansing), is intended to be a veteran, peer-outreach, support program and operates by training veterans to provide support and linkage to needed resources for returning civilian soldiers.⁵² The program's goals include improving treatment entry, adherence, and clinical outcomes and reducing suicide.⁵⁰ The program is based on the theory that for returning soldiers, peer-to-peer "buddies" can be uniquely positioned to offer emotional support and resources because they understand the experience of war, which, in turn, may help reduce the stigma associated with seeking mental health care.^{53,54}

Program volunteers are divided into two groups: "Buddy Ones" and "Buddy Twos."⁵³ According to program developers, all returning soldiers are assigned a "Buddy One." This is a veteran from a National Guard unit who has received training in peer support and systematically makes contact (via telephone) with each of his or her assigned veterans to try to identify those who might benefit from further evaluation or referral.^{53,55} Once soldiers in need are identified, Buddy Ones encourage registration and entry into Veterans Administration Hospital or military programs, develop strategies to enhance enrollment in community treatment programs, and support adherence after treatment is begun.⁵⁰ The Buddy One tier is operated and overseen by MI ARNG.⁵⁰

"Buddy Two" volunteers are veterans from outside the National Guard who are intended to serve as backup for the Buddy Ones.⁵⁰ They receive more intensive training in motivational interviewing and local resources and also receive weekly telephone supervision. These Buddies visit armories during drill weekends, are available by telephone to all soldiers, and work with individuals who are beyond the Buddy Ones' scope of training.^{50,53,55,56} Buddy Twos are overseen by University of Michigan staff.⁵³

As of October 2010, the Buddy-to-Buddy program had trained about 350 Buddy Ones and 32 Buddy Twos; the program is available only in the State of Michigan.⁵⁰ One published journal article on the program does not state the number of program participants who have been served, but notes that buddies have referred more than 20% of participants to formal treatment, indicating that a previously unmet need is being addressed by the program. That article reported that 53% of participants have used resources or services suggested by their assigned buddy.^{50,53} Based on the program's success, the developers recommended expanding the initiative to a national program for all returning citizen soldiers and urge that "these efforts be linked with evaluation outcome assessments."^{50,53} Program developers stated in 2010 that program referrals that had been made were "evaluated in greater detail and longer-term outcome evaluations are being proposed."⁵⁰

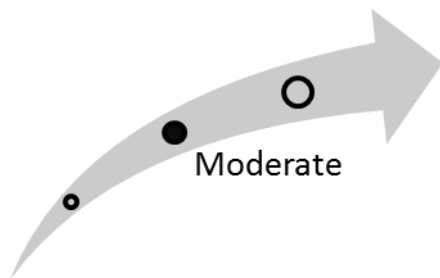
Current Approach to Care

Although both medical and psychological interventions for PTSD and clinical depression are available, only about half of citizen soldiers returning from war with these conditions seek or receive these interventions. Of soldiers referred via the Post Deployment Health Assessment screening process, only 54% follow through with a mental health visit, and only 30% report

receiving minimally adequate treatment.⁵⁰ The majority of reserve soldiers who seek care do so in the civilian sector, rather than the military sector, which may be because of a lack of military medical/psychiatric facilities in many civilian communities.^{50,57} Outcomes in this population remain poor, and the Buddy-to-Buddy program is intended to mitigate some of the barriers that exist for returning civilian soldiers who need medical or psychological intervention.

The success of the Buddy-to-Buddy program relies on its ability to match veterans in need with appropriate mental health services. Therefore, medical and psychological interventions are necessary complements to this program, as are local community resources that are intended to aid veterans in adjusting to life back home.

Figure 4. Overall high-impact potential: citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans



Experts agreed that the unmet need this program seeks to address is vast and important, that this program is likely to meet this need, and that it may have particularly positive impacts on health disparities. However, because the service is intended to link patients to existing services, experts did not believe that that this program would particularly disrupt current health care infrastructure or patient management models, other than potentially increasing patient volume in treatment centers. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.⁵⁸⁻⁶⁴

Experts strongly agreed that the unmet need for linking citizen soldiers with mental health services is important, because of the size of the affected patient population, the current underuse of mental health services by this population, and the negative impact that mental illness can have on soldiers, their families, and society. Experts were optimistic that this program has potential to improve health outcomes because it is intended to link patients with extant and proven services and interventions and because data collected thus far have been positive, although a couple of experts did note the need for longer-term or more rigorously designed trials.

Most experts thought that this program would be particularly effective in reducing health disparities across several dimensions, citing the following rationales: (1) low-income and minority individuals are disproportionately represented in the military, and these groups are affected by health disparities; (2) the program is intended to increase access to and awareness of mental health services, potentially reducing some barriers to care experienced by veterans; and (3) the program's peer-to-peer nature may be able to address health care inequalities that stem from the cultural differences of certain groups.

Experts generally did not think that this program would significantly disrupt the current health care infrastructure or the ways in which clinicians manage patients. Because the program is

designed to link patients with currently available services, its greatest impact would be a potential increase in the volume of patients seeking mental health services, most experts thought. Similarly, most expert comments reflected the view that clinicians and providers would readily accept this program, because it requires little work on their end and could increase the number of patients who are linked with appropriate care. Similarly, most experts thought the program would be accepted by the intended patient population, especially because the data (although limited) thus far suggest that soldiers in the program generally feel comfortable talking to their buddy about mental health issues.

Experts were divided on how this program would affect health care costs. On one hand, if the program is proven effective in increasing patient use of services, an increase in short-term costs could occur as new patients enter the health care system. However, if more patients with mental health conditions are appropriately managed, long-term costs associated with untreated mental health conditions may be reduced.

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